Thermal ablation of liver tumors

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GENERAL INTRODUCTION

INTRODUCTION

The Liver

The liver is the largest intra-abdominal organ located in the right upper abdomen. It has a wide range of functions, including detoxification of the blood, protein synthesis and it storages and producing bile. Unlike most other organs, the liver has two major sources of blood; (1) the portal vein, which carries blood from the digestive system to the liver and (2) the hepatic artery, which supplies the liver with oxygen-rich blood from the heart. Approximately 75% of the liver's blood supply comes from the portal vein. Most of the blood drains away from the liver through three hepatic veins (the right, middle and left hepatic veins) found inside the liver. The liver is mainly constructed of hepatocytes that account for approximately 80% of its mass [1].

Liver tumors; primary and secondary

Tumors are abnormal masses of tissue that form when cells begin to reproduce at an increased rate. Both noncancerous (benign) and cancerous (malignant) tumors can develop in the liver. Primary liver malignancies are tumors that originate from the hepatocytes (hepatocellular carcinoma or HCC) or from the biliary tract (cholangiocarcinoma, gallbladder cancer). Most patients with primary liver cancer have suffered previously from liver disease such as chronic hepatitis, cirrhosis or, in the less developed world, have been exposed to poisons from plants (aflatoxins) [2,3]. Worldwide, primary liver cancer is the third most common cause of death from cancer. Secondary liver tumors are tumors (or metastases) that spread to the liver from another primary tumor site elsewhere in the body. Tumors metastatic to the liver are more encountered than primary tumors. The most common sites of primary tumor are breast, lung, and especially colorectal cancer [4]. The high incidence of hepatic metastases have been attributed to two mechanisms. First, the dual blood supply of the liver from the portal and systemic circulation increases the likelihood of metastatic deposits in the liver. Second, the hepatic sinusoidal epithelium has fenestrations that enable easier penetration of metastatic cells into the liver parenchyma [2,3]. Tumors that spread to the liver via the blood (hematogenous) from the colon or the rectum are called colorectal liver metastases (CRLM). In the Netherlands, secondary liver cancer is about 30 times more common than primary liver cancer [5].

Benign liver tumors are tumors that can originate from the hepatocyte (focal nodular neoplasm (FNH) and hepatocellular adenomas (HCA)) or they are composed of multiple vascular channels lined by endothelial cells (hemangiomas). Hemangiomas are the most common benign primary hepatic neoplasms, often discovered incidentally. Hepatic hemangiomas can be divided into two major groups: capillary hemangiomas and cavernous hemangiomas. These tumors most frequently affect females (80%) and adults in their fourth and fifth decades of life [6,7]. In most of the cases they are small and asymptomatic. Large hemangiomas may cause symptoms such as abdominal pain, jaundice, and a palpable mass resulting from pressure effect on adjacent organs or partial infarction within the tumor. Infrequently, spontaneous rupture of hemangiomas can result in hemoperitoneum and hemobilia, and thrombocytopenia resulting from sequestration and destruction of platelets in large hemangiomas, known as Kasabach–Merritt syndrome which is seen occasionally in children. While surgical resection is mandatory in the presence of these acute medical situations, radiofrequency ablation (RFA), transcatheter arterial embolization (TAE), steroid treatment, radiation therapy, and hepatic arterial ligation have also been reported in the management of large symptomatic hepatic hemangioma. However, due to their paucity, larger series on these treatment modalities are lacking [8].

Colorectal liver metastases

Colorectal cancer is the second most common cause of cancer death in developed countries and the third most common malignancy worldwide [5,9]. In 20-25% of patients with colorectal carcinoma (synchronous) liver metastases are present at the time of diagnosis of the primary tumor [10-13]. Another 20-30% of patients develops (metachronous) liver metastases and these usually arise within 3 years after treatment of the primary tumor [5,14]. Five year survival of patients without distant metastasis at the time of diagnosis is 60-95%. When synchronous liver metastasis are present this drops dramatically to 8% [15].

It is important to evaluate every patient with CRLM individually for potentially curative options. This evaluation should be conducted by a specialized hepatobiliary multidisciplinary tumor board consisting of hepatobiliary surgeons, medical and radiation oncologists, gastro-enterologists, pathologists and both diagnostic and interventional radiologists.

Treatment of colorectal liver metastases

Surgical resection represents the historical standard and treatment of first choice of CRLM with 5-year overall survival (OS) reaching 35-60% [16,17]. Thermal ablation is a valuable adjunct to resection in otherwise unresectable patients. Clear definitions of what is regarded as resectable are lacking and vary dramatically from center to center on the basis of aggressiveness of the surgical team and the perception of the medical oncologist on when to refer patients [18]. The guideline for resectability used to be straight forward: ≤3 metastases in the same lobe without extrahepatic disease and the ability to achieve a tumor free margin of at least 1cm [19]. Because it became clear that patients who do not meet these guideline criteria can also benefit from surgical resection, resulting in an improved overall survival compared to systemic chemotherapy or best supportive care, these traditional guidelines have been abandoned. To achieve consensus, several societies for surgical oncology and hepatobiliary surgery have previously attempted to postulate resectability criteria [20,21]. The future liver remnant is of major importance. For large resections the quality of the future functioning liver remnant is a major prognostic factor to predict liver failure. For patients with normal liver parenchyma, up to 80% of the liver volume can safely be excised, because of the excellent regenerating abilities [22-27]. For patients pretreated with chemotherapy or co-existing liver impairment this percentage is considerably lower [26]. Portal vein embolization of the (most) affected liver lobe is an established technique to induce contra-lateral hypertrophy with the aim to increase the future liver remnant and hence the safety of the surgical procedure [22,23].

Despite broadening the resectability criteria, still approximately 70–80% of patients with metastases confined to the liver are considered unsuitable candidates for resection, owing to the tumor anatomy (number, size and/or locations), extensive extrahepatic disease, comorbidities and/or an impaired general health status. Thermal ablation allows parenchymal preservation, management of small-volume disease in patients who are otherwise unfit to tolerate larger liver resections, and repeated management of recurrences [28-30].

Local therapy of colorectal liver metastases; image guided (thermal) ablation techniques

Cryoablation was the first ablation modality used to treat CRLM. Due to a relatively high local recurrence rate and, more importantly, the associated morbidity, this technique was substituted by RFA in most centres [31,32]. Currently, the two most commonly employed energy sources are microwave ablation (MWA) and RFA. In RFA heat distribution is primarily based on passive conduction from a small zone of active heating around the needle electrodes. Peri-electrode charring and tissue vaporization will increase tissue impedance and hence decrease conduction at a distance from the electrodes. Microwave ablation utilizes dielectric hysteresis to produce heat. Tissue destruction occurs when tissues are heated to lethal temperatures from an applied electromagnetic field, typically at 900–2500 MHz. Polar molecules in tissue such as H_2O are forced to continuously realign with the oscillating electric field, increasing their kinetic energy and, hence, the temperature of the tissue. Tissues with a high percentage of water (as in solid organs and tumors) are most conductive to this type of heating [13]. Theoretical benefits of MWA over RFA include larger ablation volumes, shorter duration, no charring and electrical insulation, and no heat-sink effect [33]. RFA has shown promising results in the recent literature. It is a procedure with a relatively low complication rate (10%, mostly minor complications that are often unnecessary to treat) and a very small risk of death (1%), notably when compared with resection

[28,34]. Five-year survival following ablation varies between 17 % and 51 % [9]. MWA is an ablation source which is increasingly used in daily clinical practice, although long term results are limited available. Reported overall survival at Five-years is 18-56% [35-37].

Thermal ablation causes focal destruction of tissue, and when coupled with imaging guidance, this targeted destruction can be aimed at a particular metastasis. Similar to surgical resection, an important prerequisite for all ablation techniques is the coverage of all tumor cells, with tumor size representing the most important limiting factor. A new, non-thermal technique called irreversible electroporation uses electric fields to cause cell death without apparently harming tissue protein architecture that makes up structures such as bile ducts and vessels [38]. This non-thermal technique is beyond the scope of this thesis.

There are different approaches for ablation of liver metastasis. They can be treated intra-operatively using ultrasound-guidance or they can be treated percutaneous using either ultrasound (US) or, more commonly, using computed tomography (CT). However, on non-enhanced CT, tumor tissue and ablation zones are hardly visible in many cases. Therefore, during CT-guided thermal ablation the delineation of tumor tissue and the induced coagulation zone is often limited to a time window after the application of intravenous contrast media. Consequently, having reached the maximum dose of intravenous contrast material after one or two injections, repetitive monitoring during the intervention is restricted and in most centers limited to injection before the procedure (treatment planning). This is a major drawback, since dynamic and real-time tumor delineation during probe advancement and during probe repositioning is key to precise probe placement. New techniques to improve visualization during percutaneous ablations, such as positron emission tomography (PET) CT-guided percutaneous ablation and US-CT/ Magnetic resonance imaging (MRI) image fusion are promising [39,40].

Local site recurrences: imaging and treatment

Although the results of thermal ablation are approaching the results of surgical resection [41-43], the frequency of local site recurrence (LSR), especially for percutaneous procedures, is still considered relatively high (5-10% for lesions <3cm and >10% for lesions >3cm in diameter) [44,45] and needs to be improved. A precise imaging assessment of the therapeutic response and of any complications is mandatory after ablation. Early detection of residual tumor and local tumor progression is crucial in the decision whether or not to re-ablate. At most institutions, standard contrast-enhanced CT is used to evaluate the technique effectiveness; however, it is difficult to differentiate post-treatment changes from residual tumor [46,47]. Other techniques for follow-up are available. MRI and contrast enhanced ultrasound (CEUS) may be an alternative for follow up evaluation [48-52]. Dual-energy CT (DECT) is a relatively new technique that enables more specific tissue characterisation of iodine-enhanced structures because of the isolation of iodine in the imaging data [46]. 2-[fluorine 18]-fluoro-2-deoxy-D-glucose (FDG) PET imaging for the detection of liver metastases from colorectal, gastric, and oesophageal cancers has inferior sensitivity especially for smaller lesions and metastases previously treated with chemotherapy. Nevertheless, specificity for malignancy is superior to CT and MRI for the presence of vital tumor tissue and the technique is of value for detection of extrahepatic disease [51]. Instead of the traditional anatomic imaging, it visualizes glucose metabolism of tumor cells. Since metabolism is increased in tumor sites, FDG-PET has proven a valuable tool to detect malignancies throughout the body [51,52]. The images of the FDG-PET can be combined with CECT to provide accurately fused functional and morphological data sets in a single session [53]. Several studies showed superiority of PET-CT in identifying local site recurrences compared with CECT with a sensititvity and specificity of 95% and 100% (PET-CT) compared to 83% and 100% (CECT) [52, 54,55].

AIMS OF THE THESIS

The primary objective of this thesis was to assess the long term results after thermal ablation of liver metastases from colorectal cancer, to broaden the indications, and to improve the outcome by enhancing lesion conspicuity during ablation of CRLM and their local site recurrences. Besides analysing malignant liver tumors, the focal ablative treatment of symptomatic, inoperable, benign lesions was one of the aims.

THESIS OUTLINE

In chapter 2.1 the long-term results and prognostic factors of radiofrequency ablation (RFA) for colorectal liver metastases (CRLM) in a high-volume single center with >10-years of experience is analysed. One-hundred patients with unresectable CRLM underwent a total of 126 RFA sessions (237 lesions). Patient characteristics, lesion characteristics (size, number and location) and procedure characteristics (percutaneous or intraoperative approach) were used as variables; major and minor complications were carefully noted. Local control, mean survival-time and overall survival were statistically analysed.

In chapter 2.2 the purpose was to retrospectively analyse the safety and efficacy of RFA versus MWA in the treatment of unresectable colorectal liver metastases in proximity to large vessels and/or major bile ducts.

Chapter 2.3 is designated to the summary of a meta-analysis to assess safety and outcome of RFA and MWA as compared to systemic chemotherapy and hepatic resection in the treatment of colorectal liver metastases.

In chapter 3.1 the incidence of local site recurrences of CRLM after the treatment with RFA is examined. Also the median overall survival and overall survival after retreatment of those local site recurrences was analysed differentiating between synchronous versus metachronous CRLM, small versus large lesion size (0-3cm versus > 3cm) and the number of lesions treated.

In chapter 3.2 we assess criteria for FDG PET-CT image interpretation following RFA with special interest to the interval between treatment and recurrence and provide suggestions to define a timetable for follow-up detection of LSR.

In chapter 4.1 we describe the feasibility and accuracy of transcatheter CT arterial portography (CTAP) or transcatheter CT hepatic arteriography (CTHA) as an imaging modality for preprocedural needle position planning and intraprocedural real-time image-guider to facilitate percutaneous ablation of liver tumors as well as to create an endpoint after a technically successful ablation, allowing additional overlapping ablations within the same session.

In chapter 4.2 we report nine patients with post-ablation local site recurrences, in whom transcatheter CTHA allowed differentiation of recurring and residual tumor tissue (incomplete ring enhancing lesion) from tumor-free non-enhancing scars. Using CTHA it is feasible to plan and guide percutaneous retreatment and to confirm technical success without having to use oversized re-ablations or jeopardizing patients renal function.

In chapter 5.1 the objective was to evaluate the safety, feasibility and local effectiveness of a novel bipolar plan-parallel expandable radiofrequency ablation system (bipolar RFA) for larger liver tumors.

In chapter 5.2 we describe the first clinical experience with bipolar radiofrequency ablation for symptomatic giant hepatic hemangiomas (GCH).

In chapter 5.3 two cases are presented in which bipolar RFA of very large symptomatic GCHs (15.7cm and 25.0cm) was complicated by heme pigment induced acute kidney injury due to massive intravascular hemolysis caused by heat. In the treatment of large GCHs these cases suggest a reduction of the number and duration of the ablation should be reduced to the minimum necessary and caution is warranted.

The last chapters 6 and 7 concern the conclusions and summary of the thesis respectively in English and Dutch.

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